PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000188	19.01.2005	17.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/72, A61K39/00

Applicant
NEUROTARGETS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17-32 with respect to industrial applicability; 1-32, 48-100 partially

because:

☒ the said international application, or the said claims Nos. 17-32 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-32, 48-100 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-32, 48-100 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-100
	No:	Claims	
Inventive step (IS)	Yes:	Claims	33-47, 96-100
	No:	Claims	1-32, 48-95
Industrial applicability (IA)	Yes:	Claims	1-16, 33-100
	No:	Claims	

2. Citations and explanations

see separate sheet

Ad Section III: Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Present **claims 1-32 and 48-100** relate to the use of a product or a method employing the product wherein the product is defined by reference to a desirable characteristic or property, namely its agonistic activity. This is in contrast to the requirements of Art. 6 PCT, because the result-to-be-achieved type definition does not allow the scope of the claim to be ascertained (see also PCT Guidelines, 5.35). The fact that the product to be used could be screened (using the method of claim 33) does not overcome this objection as the skilled person would not have knowledge beforehand, except for the agonist AR-M1896, as to whether it would fall within the scope claimed. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search for these claims (PCT Guidelines, 9.19).

The search of **claims 1-32 and 48-100** was thus restricted to those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the GALR2 agonist AR-M1896.

2) **Claims 17-32** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. In this respect the following should be noted:

For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Ad Section V: Reasoned statement with regard to novelty, inventive step or

industrial applicability

The following comments are made solely with respect to the claims insofar they relate to the GALR2 agonist AR-M1896 (see also Section 3, point 1).

Claims 1-16 relate to the use of a GALR2-specific agonist (i.e. AR-M1896) in the preparation of a medicament for the prevention or treatment of brain injury, damage or disease.

The prior art does not disclose such uses. Hence the claims formally meet the requirements of Art. 33(2) PCT.

The application, however, is devoid of any examples which would clearly show that AR-M1896 actually has an effect in the claimed diseases.

The application provides evidence that AR-M1896 is effective in reducing cell-death in organotypic cultures from wild type animals when co-administered with staurosporine. Moreover, it could be shown that AR-M1896 was also effective in reducing staurosporine-induced cell-death in galanin knock-out cultures.

In further experiments it could be shown that hippocampal organotypic cultures from galanin over-expressing animals were better protected from fibrillar Aβ(1-42)-induced cell death when compared to wild-type controls. In addition it was shown in an MS model that galanin over producing animals failed to develop symptoms of the disease.

While these experiments show that galanin may be involved in the development of various diseases of the nervous system, a direct link between the specific GALR2 and the diseases has not been established.

Hence **claims 1-16** broadly seeking protection for the use of a specific GALR2 agonist for the treatment of all kinds of nervous diseases cannot be considered supported by the description. An inventive step, thus, cannot be acknowledged for these claims.

Claims 17-32 which are directed to a method for preventing or treating brain injury, damage or disease comprising administering an effective amount of the GALR2 agonist AR-M1896 and **claims 48-95** directed to a pharmaceutical composition for use in the prevention or treatment of brain injury, damage or disease comprising AR-M1896 formally meet the requirements of Art. 33(2) PCT.

An inventive step, however, cannot be acknowledged for these claims following the same arguments as given above with respect to claims 1-16.

Claims 33-47 which are directed to a method of screening for a candidate brain injury treatment compound is considered to meet the requirements of Art. 33(2)(3) PCT.

Claims 96-100 which are directed to a method of inhibiting cell death employing the GALR2 specific agonist AR-M1896 are also considered to meet the requirements of Art 33(2)(3) PCT.